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REVIEW

Aortic Calcification

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Objectives. *Vascular calcification is a complicating factor observed in advanced atherosclerosis. This review summarises the present knowledge regarding abdominal aortic calcification.*
Design. *Literature review.*
Methods. *A literature review was carried using MEDLINE and PUBMED with the search terms 'abdominal', 'aortic' and 'calcification'. Articles were assessed for data regarding mechanisms, measurement, risk factors and outcomes of aortic calcification.*
Results. *Thirty relevant studies were identified. These demonstrated a positive correlation between abdominal aortic calcification and the following factors: older age, hypertension, and smoking. Further studies are required to critically assess other risk factors such as gender, diabetes mellitus and renal failure. Calcification of the abdominal aorta is associated with an increased risk of mortality, coronary heart disease and stroke.*
Conclusion. *Aortic calcification predicts an increased incidence of cardiovascular events, however, the reasons for this association requires further investigation. Accurate measurement of aortic calcification is likely to be increasingly used to determine the risk of cardiovascular events.*

Keywords: Vascular calcification; Aortic; Patient outcomes.

There is great interest in vascular calcification in terms of risk factors and subsequent outcomes. Studies in the coronary arteries demonstrate an association between calcification and cardiovascular events, in particular myocardial infarction.[1] For example, a meta-analysis by O'Malley *et al.*[2] demonstrated that coronary artery calcification was associated with a 8.7 fold increased risk of cardiac events and 4.2 fold increased risk of death or myocardial infarction. Other studies examining the coronary circulation demonstrate a correlation between the degree of calcification and the severity of atherosclerosis and clinical events.[3–10] Similar relationships between calcification and cardiovascular events have been demonstrated in other vascular beds, such as the aortic arch[11–13] and the thoracic aorta.[14–16] Whether the calcification has a direct detrimental effect or is simply a marker of atherosclerotic burden is unknown.

Unlike the coronary circulation, relatively little is understood about the importance of calcification within the abdominal aorta. Similar to the coronary circulation, aortic calcification likely influences subsequent cardiovascular events such as aortic occlusion, aneurysm development and distal embolisation.[17,18] Calcification within the aorta also impacts on medical and surgical treatment for example by impairing the outcome of aortic stenting and aneurysmal repair.[18] To better understand the significance of abdominal aortic calcification, this review will focus on the measurement, risk factors and outcomes of abdominal aortic calcification.

To appreciate the significance of abdominal aortic calcification, an understanding of the mechanism of vascular calcification is required. Seminal work carried out by Virchow and Rokitansky in the 19th century showed that fully formed bone tissue was present in atherosclerotic arteries.[19,20] However, it is now recognised that vascular calcification involves a complex, regulated process of biomineralisation.[21,5] Although the precise mechanism of vascular

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calcification is yet to be elucidated, it most likely involves some elements of bone metabolism.[4,22] Broadly, two theories have been suggested, the active model which incorporates analogous cell types and cytokines to those involved in bone remodelling and the passive physiochemical model. Currently, most support is for the active model (see review by Doherty *et al.*[22]).

An understanding of the histopathology of vascular calcification is necessary to appreciate its detection by imaging modalities. Vascular calcification is classified as intimal and medial, according to the arterial layer in which the calcification occurs.[4,6,23,24] Both types are observed in the abdominal aorta.[4,21] Most studies to date have concentrated on intimal calcification due to its association with atherosclerosis. Medial calcification or Monckeberg sclerosis occurs independently of atherosclerosis.[22,23,25] This form of calcification is commonly found in patients with renal failure and diabetes mellitus and has, therefore, been suggested to occur as a result of a disturbance in metabolic, electrolyte and pH balance.[22,26] It is thought that this form of calcification has a predilection for arteries less prone to atherosclerosis. Medial calcification is rarely seen in the coronary arteries but does affect the abdominal aorta.[4,22] There is often a lack of differentiation between the two types in the literature, likely as a result of the limitation of imaging modalities to differentiate the two, which requires histopathology.

Methods

Study identification

To identify appropriate studies, a search was performed using the MEDLINE and PUBMED database. The search included the primary descriptors abdominal, aortic and calcification. The search was limited to articles in English. One hundred and seventy-eight suggestive articles were located and the corresponding abstracts were read to identify those that were appropriate. The reference lists of these articles were used to identify additional articles missed by the computerised database search.

Inclusion and exclusion criteria

To be included in this review, the study had to provide data in relation to the method of measurement, quantification, the associated risk factors or the outcome of abdominal aortic calcification. Studies published prior to 1984 were excluded from the review. From the initial, 178 articles identified from the MEDLINE/PUBMED searches, a total of 30 papers were accepted as providing relevant data.[3,16,27–54]

Measurement of Aortic Calcification

The measurement of arterial calcification may become a significant tool to predict clinical events associated with the abdominal aorta. Three imaging methods have been employed to detect, quantify and define calcification (Table 1[3,16,27–54]). These include electron beam computed tomography (EBCT), computed tomography (CT) and plain X-ray. Presently no modality has been accepted as the gold standard for the measurement of abdominal aortic calcification, consequently there is little assessment of the sensitivity and specificity of these techniques.

Electron beam computed tomography (EBCT)

EBCT is a non-invasive method of detecting calcification and is increasingly used to assess coronary arteries.[2,55,56] The advantages of EBCT is that it allows very rapid acquisition of images, preventing image blurring and accurate visualisation of small calcific deposits in the coronary arteries without utilising contrast media.[57,58] Within the coronary circulation EBCT detection of calcification has been shown to correlate with the angiographic severity of coronary artery disease (CAD).[57,58] The Expert Consensus Document of the American College of Cardiology/American Heart Association states that the sensitivity and specificity of EBCT to detect coronary artery stenosis or occlusion demonstrated on angiography is 90.5 and 49.2% in their evaluation of 3683 patients enrolled in 16 studies.[59]

Four studies using EBCT to quantify abdominal aortic calcification were identified.[3,16,27,28] Each investigator used a different scoring system to quantify the severity of aortic calcification and examined different sites within the aorta. The scoring method in these studies is similar to that employed in the coronary circulation, but varies between investigators. For example, Allison *et al.*[28] utilised a modification of the Agatston method whereas, Reaven and Sacks[27] utilised a calcium score based on the sum of individual lesions along the scanned section of the aorta. These studies did not report the reproducibility of their method of analysis, however, Kuller *et al.*[3] in their 11-year prospective study reported high reproducibility with an inter-class correlation of 0.98.

Table 1. Studies measuring abdominal aortic calcification

References	Modality	Subjects	Quantification of calcification	Region assessed
[3]	EBCT	169	Calcium score	Aortic arch to iliac bifurcation
[16]	EBCT	99	Calcium score	Abdominal aorta
[27]	EBCT	245	Calcium score	Abdominal aorta (right kidney to iliac bifurcation)
[28]	EBCT	650	Calcium score	Diaphragm to iliac bifurcation
[29]	CT	129	Calcification grade	Coeliac artery origin; left renal vein level; aortic bifurcation
[30]	CT	40	Calcification volume	SMA to iliac bifurcation
[31]	CT	137	Aortic calcification area index (%)	Above common iliac bifurcation
[32]	CT	116	Aortic calcification volume (%)	Above common iliac bifurcation
[33]	CT	20	Atherosclerosis index	Abdominal aorta (L3 or L4)
[34]	CT	405	Degree of calcification (%)	Aortic arch to bifurcation
[35]	CT	257	Calcification grades	SMA to bifurcation
[43]	CT	29	Calcification volume (%)	At and above common iliac bifurcation
[48]	CT	26	Aortic calcification index	Abdominal aorta
[49]	CT	152	Vessel wall or thrombus calcification	Abdominal aorta
[50]	CT	102	Aortic calcification index	Abdominal aorta
[51]	CT	36	Aortic calcification index	Abdominal aorta
[36]	X-ray	89	Calcification grades	Abdominal aorta
[37]	X-ray	79	Calcification grades	Abdominal aorta (T12–S1)
[38]	X-ray	2151	Calcification grades	Aortic wall at each vertebral segment (L1–L4)
[39]	X-ray	97	Calcific deposit length (mm)	Abdominal aorta (L1–L5)
[40]	X-ray	554	AAC index	Abdominal aorta (L1–L4)
[41]	X-ray	720	Aortic length involved	Abdominal aorta (T12–S1)
[42]	X-ray	177	Calcification grades	Abdominal aorta
[44]	X-ray	758	Calcification grade	Abdominal aorta
[45]	X-ray	773	Calcium score	Abdominal aorta
[46]	X-ray	110	Semi-quantitative score	Abdominal aorta
[47]	X-ray	182	Presence of calcium	Abdominal aorta
[52]	X-ray	2467	Calcium score	Abdominal aorta
[53]	X-ray	2515	Calcium score	Abdominal aorta
[54]	X-ray	6913	Calcium score	Abdominal aorta (L1–L4)

AAC, abdominal aortic calcification; L, lumbar vertebrae; SMA, superior mesenteric artery; T, thoracic vertebrae; S, Sacrum.

Computed tomography (CT)

Twelve studies have used CT to measure abdominal aortic calcification,[29–35,43,48–51] however, there is variation in the grading and location of these measurements. For example, Kimura *et al.*[31] quantified the aortic calcification as a percentage of the cross sectional area of the aorta whereas, Miwa *et al.*[32] although using a similar quantification method, expressed the calcification as a percentage of the aortic volume in their prospective study. A retrospective study graded the calcification as a percentage of the aortic circumference.[29] Most investigators did not comment on the reproducibility of their measurement method, however, Miwa *et al.*[32] reported an intra-observer and inter-observer coefficient of variation of 4.4 and 5.1%, respectively.

X-ray

The simplest method of detecting abdominal aortic calcification is with plain abdominal X-ray. Quantification using this technique, however, is highly varied, with a number of grading systems being reported. Our review identified 14 studies which utilised X-ray to measure abdominal aortic calcification.[36–42,44–47,52–54] In a study by Kawaguchi *et al.*,[36] grade 1 was equivalent to no calcification, grade 2 described patchy calcification and grade 3 denoted calcification along the entire abdominal aorta giving it a lead pipe shape on X-ray. Jie *et al.*,[37] however, specified grade 0 as having no calcification and grade 4 as having the aorta outlined with calcification. In the study by O'Donnell *et al.*[38] the calcification grade was dependent on the longitudinal length of aortic wall affected. Scores ranged from grade 0, which had no calcific deposits to grade 3 that had two thirds or more of the longitudinal wall calcified. The accuracy and reproducibility of the techniques employed were discussed in many of the studies,[38,40–42,44–47,52,53] although not rigorously. However, four studies failed to discuss this issue.[36,37,39,54] For example, Hak *et al.*[41] required two independent observers to examine the films and be in consensus regarding their reading.[41] The investigators reported a percentage of agreement for absence versus presence of progression of calcification of 88% with a k statistic of 0.74. Nakamura *et al.*[39] on the other hand measured the length of abdominal aortic calcification by tracing the regions onto tracing

paper. Although an electronic calliper with a resolution of 0.01 mm was used, the author did not report the reproducibility or accuracy of this method.[39]

Abdominal aortic region assessed

The region of the abdominal aorta in which calcification is quantified is likely to have a significant impact on the score achieved. In general, atherosclerosis and, therefore, calcification is more common at arterial bifurcations.[60] Some studies failed to specify the regions of the abdominal aorta that were analysed.[34,36,42,45,46,48,50,51] In studies that did specify the region investigated, there was marked variation in the site examined. For example, Kimura *et al.*[31] assessed the calcification just above the bifurcation of the common iliac arteries, while Reaven and Sacks[27] scanned from the kidney to the iliac bifurcation.

Clinical Determinants of Abdominal Aortic Calcification

The incidence and severity of abdominal aortic calcification was studied in relation to a variety of risk factors in the articles reviewed.[3,27–29,31,32,34,35,38,40–43,47,48,50,51] The heterogeneity in the studies identified hampers the synthesis of results in a systematic manner. This heterogeneity arises from the variation in study design and outcome measures used to report findings.

A number of sources contribute to the variability in study design. Firstly, retrospective, prospective and cross sectional studies were included in the review. Secondly, the cohorts under investigation varied between the studies. For example, Kuller *et al.*[3] had a cohort of women going through menopause, while Kiel *et al.*[40] looked at the Framingham Heart Study population. Thirdly, there was variability in the detection and quantification of aortic calcification (Table 1). The imaging modalities used and the sections of the abdominal aorta studied varied between the studies. The quantification of calcification also varied, with subjective and objective measurements carried out. Fourthly, a majority of studies considered more than one clinical determinant in assessing for a relationship to abdominal aortic calcification.

The outcome measures used to report findings also varied between studies. Measures used included relative risk (RR), odds ratio (OR), hazard ratio (HR) and correlation coefficients. A majority of studies also failed to publish unanalysed data. In the following section, we discuss the findings of these studies in relation to the different risk factors for abdominal aortic calcification. Due to the variation in presentation of data and outcome measures, it is not possible or useful to combine data from these studies. Instead we report the findings of the different studies in relation to there quality.[3,27–29,31,32,34,35,38,40–43,47,48,50,51]

Age

The atherosclerotic process begins during childhood and may progress to form an advanced atheroma with some lesions becoming calcified.[28] Therefore, age would be expected to be an important determinant of the presence and severity of abdominal aortic calcification. Five studies examined the relationship of aortic calcification to age.[27,28,32,38,40] The finding across all the studies is that abdominal aortic calcification is positively related to age. In two studies, it was possible to separate the cohort into older and younger participants with high and low calcification levels.[27,32] The larger of these studies, conducted by Reaven and Sacks[27] had 245 participants, with calcification measured using EBCT. This study revealed that elderly people (age $\geq$61 years) had more severe aortic calcification.[27]

The remaining three studies each contained a larger number of subjects but did not present their data in a manner enabling separation based on age or calcification severity.[28,38,40] In the study by Allison *et al.*,[28] the results on the prevalence and severity of abdominal aortic calcification were based on age specific groups. However, the authors failed to indicate how many patients were in each age specific group. The investigators demonstrated a very important influence of age on both prevalence and severity of aortic calcification in both genders (Fig. 1). For example, at age $<$50 years the prevalence of abdominal aortic calcification is 16 and 20% in women and men, respectively. This increases to 93 and 98% by age $>$70 in women and men, respectively. The odds ratio (OR) for presence of abdominal aortic calcification per 10 years was 5.5 for women and 5.6 for men (95% CI, 3.4–9.0 and 3.6–8.8, respectively).[28] While O'Donnell *et al.*[38] in their much larger study also showed a correlation between age and aortic calcification; however, they utilised X-ray which is a less sensitive method to quantify calcification. Similarly Kiel *et al.*[40] reported a six-fold and eight-fold increase in aortic calcification in men and women, respectively during a 25-year follow-up study. The literature search did not locate any studies showing a negative or nil correlation with age,

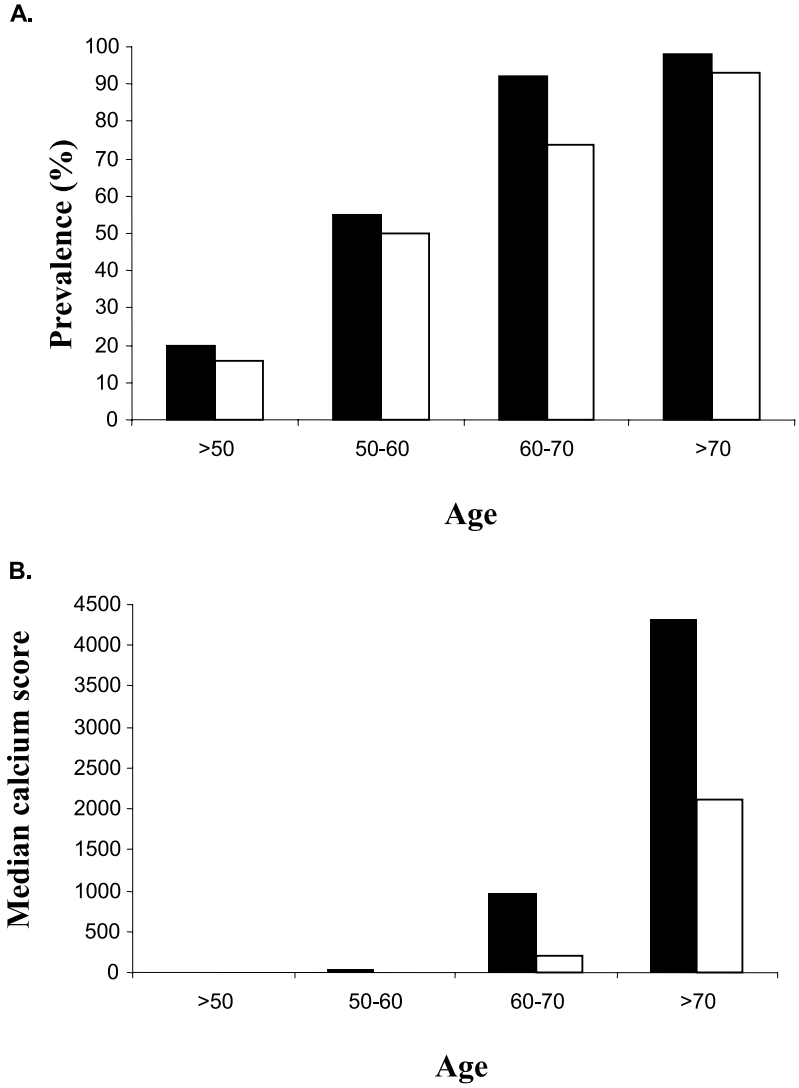

Fig. 1. Prevalence (A) and severity (B) of abdominal aortic calcification with increasing age in men (black) and women (clear). (Adapted from Allison *et al.* with permission).[28]

indicating age as an important risk factor for abdominal aortic calcification.

Gender

Males have a higher risk of atherosclerosis compared to females, therefore, gender would be expected to be an important determinant of abdominal aortic calcification.[61] In the coronary circulation, it is known that calcification is greater in men than in women.[62] Six studies reported findings with respect to gender and its relationship to abdominal aortic calcification.[3,28,35,38,40,41] Four of these studies had cohorts of both males and females[28,35,38,40] and of these only Dixon *et al.*[35] presented data in a manner allowing separation into high and low calcification levels. Dixon *et al.*[35] found that significantly more females (20%) than males (5%) 60–80 years had advanced calcification ($p<0.05$). However, they found no significant association between the presence of abdominal aortic calcification and gender.[35]

The study by Allison *et al.*[28] was cross sectional in nature and utilised EBCT. They demonstrated that the prevalence of calcification was greater in males, with 70% of men and 47% of women less than 50 years and 98% of men and 91% of women aged 60–70 years having measurable aortic calcification. The investigators also reported that the abdominal aorta was the commonest site of vascular calcification in women.[28] While the study by Kiel *et al.*,[40] which used a less sensitive imaging modality, examined

aortic calcification in the Framingham Heart Study cohort of men and women over a 25-year period.[40] Calcification progressed at similar rates in both genders, but in women there was a significant correlation between bone loss and the rate of increase in aortic calcification.[40]

Two studies examined abdominal aortic calcification in cohorts of women only.[3,41] Kuller *et al.*[3] and Hak *et al.*[41] were both population based longitudinal studies looking at the impact of menopause on aortic calcification and bone loss in women. The higher powered of these two studies was conducted by Hak *et al.*[41] In this study, 236 initially premenopausal women were followed for 9 years as well as a cross sectional study of 720 postmenopausal women.[41] From the cohort of 236 women, 59 (25%) showed progressive aortic calcification during the follow-up period. The study also investigated bone loss using metacarpal radiometry to assess the metacarpal cortical area (MCA). The loss of bone mass was positively correlated with progression of aortic calcification. The mean loss of MCA in women with progressive aortic calcification and those without was 3.2 ± 0.04 mm^2 and 2.0 ± 0.2 ($p = 0.01$), respectively.

Although relatively few studies have investigated the relationship of gender to abdominal aortic calcification critically, there is evidence to suggest that a gender difference exists. Gender may also play a role in determining the distribution of vascular calcification. Larger prospective studies of both genders are required to assess this in a more critical manner.

Diabetes mellitus

Diabetes mellitus is associated with arterial calcification, both medial and atherosclerotic intimal types.[61] Six studies were identified which analysed the relationship of abdominal aortic calcification to diabetes mellitus.[27–29,34,38,42] Of these, two studies used diabetes mellitus as a single variable under investigation.[27,42] The remaining studies analysed diabetes mellitus as one of a number of clinical determinants considered.[28,29,34,38] Five studies supported the relationship of aortic calcification to diabetes mellitus.[27,28,34,38,42]

Only one study compared abdominal aortic calcification in diabetics and non-diabetics.[42] Niskanen *et al.*[42] identified aortic calcification in 29% of diabetics and 17% of non-diabetic men ($p = 0.05$) and 26% of diabetic and 19% of non-diabetic women ($p = 0.06$) in a 5-year follow-up study. Although the investigators originally quantified the calcification into four categories, the final data is presented as the total number of patients with any calcification. Therefore, no differentiation is made in terms of the severity of aortic calcification. Reaven and Sacks[27] also assessed the impact of diabetes on abdominal aortic calcification using EBCT. They found that aortic calcification was positively related to the duration of diabetes ($r = 0.23$, $p < 0.01$).[27]

Four studies investigated the impact of diabetes mellitus as one of a number of clinical determinants under investigation.[28,29,34,38] However, diabetics have a higher incidence of other traditional cardiovascular risk factors, such as hypertension and hyperlipidaemia,[34,38] which may confound the analysis of the relationship between diabetes mellitus and abdominal aortic calcification. The limited studies carried out to date suggest that abdominal aortic calcification is more common in diabetics.[28,34,38] In contrast, Matsushita *et al.*,[29] in their assessment of a male cohort did not find a correlation between diabetes and the incidence or severity of calcification. However, this retrospective study contained the smallest cohort of subjects compared to the other studies.

Hypertension

Hypertension is a known risk factor for atherosclerosis.[17,63] Aortic calcification changes the normal vascular hemodynamics by increasing arterial rigidity.[39,46,64] Given that peripheral arterial calcification will affect the measurement of blood pressure,[39] any demonstration of an association between blood pressure and prevalence of aortic calcification does not necessarily imply a causal relationship.

Seven studies examined the relationship of abdominal aortic calcification and hypertension.[3,28,29,31,32,38,43] Two studies allowed comparison between hypertensive and non-hypertensive subjects, based on the severity of calcification.[29,31] The data from both these studies indicate that hypertensive subjects have more severe abdominal aortic calcification.[29,31] Kimura *et al.*[31] showed that in patients on haemodialysis there is also an association between abdominal aortic calcification and high systolic blood pressure. While Matsushita *et al.*[29] in their retrospective study of 129 males with abdominal aortic aneurysms (AAA), showed that calcification was more common with hypertension (at the level of the coeliac artery $p < 0.05$ and at the level of left renal vein $p < 0.0005$).

Four studies did not present data in a manner allowing comparison between hypertensive and non-hypertensive patients.[3,28,32,38,43] However, several important associations were revealed by these studies. For example, Allison *et al.*[28] demonstrated an

association between hypertension and distal aortic calcification using multi-variable logistic regression in a highly powered study using EBCT. In men the OR was 2.1 (95% CI 0.9–4.8), while in women OR was 2.6 (95% CI 1.1–6.2).[28] While O'Donnell *et al.*[34] also reported an association between systolic blood pressure and aortic calcification ($r=0.27$, $p<0.0001$). This study, although containing the largest number of subjects, utilised X-ray, a less sensitive imaging modality to quantify calcification. In contrast to the above findings, a prospective open labelled study by Arai *et al.*[43] did not detect a correlation between aortic calcification and systolic or diastolic blood pressure. However, this study only included 29 subjects.

Thus, the available studies suggest an association between hypertension and abdominal aortic calcification. Whether hypertension predisposes to aortic calcification or patients with vascular calcification have higher blood pressure readings remains to be determined.

Smoking

Cigarette smoking is a recognised risk factor for cardiovascular disease and atherosclerosis.[44,53,65] In an autopsy study carried out by Auerbach and Garfinkel,[66] a direct relationship between the atherosclerotic lesions, recorded as calcification, and smoking habits of male patients was observed. More extensive alterations were found in the abdominal aorta than in the thoracic portion and the extent of the lesions increased with the number of cigarettes smoked.[66] Five studies have looked at the effect of cigarette smoking on abdominal aortic calcification using imaging modalities.[27–29,38,44] Of these, only one looked at cigarette smoking as a single variable under investigation.[44] Witteman *et al.*[44] used plain X-ray to examine the relationship between smoking and aortic calcification in women in a population based 9-year follow-up study. Compared to those who had never smoked, the relative risk (RR) of those who smoked 1–9 cigarettes per day was 1.4 (95% CI 1.0–2.0), 10–19 cigarettes per day was 2.0 (95% CI 1.6–2.5) and >20 cigarettes per day was 2.3 (95% CI 1.8–3.0) after adjustment for age and other cardiovascular risk factors.[44] Smoking cessation over time resulted in a reduction in the RR for vascular calcification, however, significant excess risk was observed 5–10 years after quitting (RR 1.6; 95% CI 1.1–2.2).[44]

The remaining studies examined the effect of cigarette smoking on abdominal aortic calcification as one of a number of clinical determinants considered.[27–29,38] A majority of these studies showed strong evidence to support smoking as a risk factor for aortic calcification.[27,28,38] These studies all had large cohorts and those by Reaven and Sacks[27] and Allison *et al.*[28] also utilised EBCT. Although there is strong evidence to support smoking as risk factor for aortic calcification, Matsushita *et al.*[29] failed to report any correlation at the aortic bifurcation. However, this was the smallest study, with retrospective analysis of 129 subjects and subjective quantification of calcification.

Renal failure

Patients on dialysis have an incidence of cardiovascular events 10–30 times greater than those of the general population.[67] This high incidence of vascular calcification seen in patients with chronic renal failure (CRF), however, cannot simply be explained by the prevalence of atherosclerosis in this patient group. It appears likely that metabolic parameters such as hyperphosphataemia and elevated calcium–phosphorus product also plays an important role in the excess incidence of vascular calcification in this patient group.[68] Despite the convincing evidence that renal failure is a risk factor for vascular calcification, there are no studies comparing abdominal aortic calcification in patients with or without renal failure. However, four studies have examined the risk factors for abdominal aortic calcification in subgroups of patients with CRF.[31,36,47,48] These studies have demonstrated that aortic calcification is more common in patients who are on dialysis for longer periods, both peritoneal and haemodialysis.[31,36] For example, Kawaguchi *et al.*[36] found that the mean duration on dialysis of patients with grade 1 abdominal calcification was 41 months, while for patients with grade 3 calcification it was 68 months ($p<0.001$). The larger study by Kimura *et al.*[31], with a cohort of 137 haemodialysis patients, also supports this finding. They found that abdominal aortic calcification was greater with increased duration on dialysis ($p<0.01$).

The mechanisms underlying aortic calcification in patients with CRF are not completely understood. In addition to predilection for atherosclerosis and metabolic derangement, patients with CRF are commonly treated with calcium containing phosphate binders. Evidence from both animal and human studies indicate that this medication promotes aortic calcification.[65,68] In a rat model of renal failure, calcium containing phosphate binders promoted aortic calcification.[68] Similarly in a randomised controlled trial, calcium containing phosphate binders promoted aortic calcification.[65] However, the currently available human studies investigating the relationship of renal

failure to aortic calcification consist of small cohorts; thus firm conclusions are difficult to reach. Further studies with larger patient numbers are required to examine this issue more thoroughly.

Peripheral arterial disease (PAD)

Aortic calcification is a common finding in patients with symptomatic peripheral vascular disease and abdominal aortic aneurysm (AAA). Presently, there are relatively few studies that have investigated the relationship between abdominal aortic calcification and either of these two pathologies. In a study of 336 post-mortem specimens of the aorta, aortic calcification was reported to be more prevalent and more severe in patients with previous symptoms of intermittent claudication.[69] Two studies investigated the relationship between abdominal aortic calcification and peripheral arterial disease.[42,49] However, both studies consisted of small subject numbers, thus limiting the information that can be gained. Niskanen *et al.*[42] assessed a group of diabetics (type 2) and a control group over 5 years for aortic calcification using X-ray imaging. The prevalence of abdominal aortic calcification was higher in the subjects who developed intermittent claudication during follow-up than in those who were symptom free during the 5-year examination.[42] Torres *et al.*[49] demonstrated aortic calcification in all 145 patients with AAAs assessed by CT. The high prevalence of aortic calcification in patients with aneurysms simply may relate to the other risk factors for calcification in these patients. Further work is required to define the relationship between aortic calcification, aneurysm and occlusive disease.

Serum calcification markers

There are a number of lipids and proteins that have been identified as being important to the atherosclerotic and calcific process. Some of these mediators are present in measurable levels within the serum. The ability to identify patients at risk of or who already have aortic calcification using serum markers could prove to be an invaluable preventative or diagnostic tool.

Lipids

Lipids play a fundamental role in atherosclerosis and therefore would be expected to influence the development of arterial calcification.[70] Studies have shown a relationship between vascular calcification and abnormal serum lipid levels.[32] While statins, a class of lipid lowering medications, have been demonstrated to inhibit the progression of vascular calcification. It must be noted, however, that statins have pleiotropic effects unrelated to lipid metabolism.[32]

Ten studies examined the relationship of lipids to abdominal aortic calcification.[3,27,28,31,32,36,38,41–43] There is variation in the serum lipid components reported in these studies. For example, Arai *et al.*[43] reported on cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c), while Hak *et al.*[41] and Allison *et al.*[28] reported only on cholesterol. Five studies indicate that no correlation is present between abdominal aortic calcification and serum lipid components.[29,31,32,36,42] These studies all considered the effect of lipids in the setting of a multiple number of clinical determinants investigated. The studies were all relatively similar in size, however, there was marked heterogeneity in the cohorts studied.

The remaining five studies showed a correlation of abdominal aortic calcification to lipids.[3,28,38,41,43] For example, Kuller *et al.*[3] used EBCT to examine aortic calcification in 166 women. Serum concentrations of HDL were negatively associated with aortic calcification. Forty percent of women with HDL-c <60 mg/dL had a calcium score >300; while 11% of women with HDL >60 mg/dL had calcium score >300 $p<0.001$.[3] Allowing for other risk factors of aortic atherosclerosis, a 20 mg/dL increase in LDL-c was significantly associated with aortic calcification, OR 1.33 (95% CI 1.0–1.8), whereas a HDL-c increase of 10 mg/dL was negatively associated with aortic calcification, OR 0.70 (95% CI 0.47–1.0).[3] Recent studies by Allison *et al.* (personal communication) investigated cholesterol indices and their association with vascular calcification. Their study of 940 asymptomatic subjects showed that women who were not on cholesterol medication, had significant correlations between serum lipids (HDL, non-HDL and TC/HDL ratio) and calcification in the thoracic and abdominal aorta. Other larger studies by O'Donnell *et al.*[34] and Hak *et al.*[41] also support an association between aortic calcification and lipid components. One small prospective open labelled study looked at a cohort of patients with hyperlipidaemia.[43] This study indicated that abdominal aortic calcification was associated with cholesterol ($p<0.05$), HDL-c ($p<0.01$) and LDL-c ($p<0.05$).[43] However, the findings of this study may not be completely reliable, since there were only 29 subjects. The divergent findings of the studies indicate that higher-powered studies are required to clearly define the relationship between lipids and aortic calcification.

Other serum markers

Osteoprotegerin (OPG) is a bone forming protein that is involved in vascular calcification.[71] It is a soluble decoy receptor of the tumour necrosis factor receptor superfamily.[71] The suggested role of OPG in arteries is to inhibit calcification.[25] Animal studies indicate that OPG has disparate effects within bone and arteries, i.e. favouring bone formation, but inhibiting vascular calcification.[71] In studies conducted in humans, Nitta *et al.*[48] demonstrated that serum OPG concentration was independently associated with abdominal aortic calcification in 26 haemodialysis patients.[48] Furthermore, a study of over 100 patients showed a positive correlation between aortic calcification and OPG ($r=0.483$, $p<0.0001$).[50] OPG may also play a role in the high incidence of vascular calcification seen in postmenopausal women and diabetics.[22,71]

It is reasonable to suggest a role for osteopontin (OPN) in abdominal aortic calcification as it has been demonstrated within abdominal aortic atherosclerotic plaques, particularly adjacent to areas of calcification.[34] OPN is a Gla containing bone matrix protein involved in the calcification process.[22,72,73] Two studies have examined the relationship between soluble OPN and abdominal aortic calcification and found a correlation between OPN and abdominal aortic calcification in terms of progression of aortic calcification[48] and the aortic calcification index.[51]

Inflammation plays a significant role in the pathophysiology of atherosclerosis and its clinical outcomes.[39,74] Recent studies have suggested that inflammation and C-reactive protein (CRP) in particular, may result in endothelial dysfunction, an early event involved in the initiation of lesion formation, eventually leading to arterial calcification.[67] The Rotterdam Study investigated the relationship between CRP and atherosclerosis in various vascular beds.[45] An association between CRP and abdominal aortic atherosclerosis, identified as calcific deposits using plain X-ray, was demonstrated with an OR of 1.7 (95% CI 1.0–3.0) when adjusted for age, gender and smoking status and OR of 1.5 (95% CI 0.8–2.8) when adjusted for cholesterol, diabetes and hypertension. Nitta *et al.*[50] detected high CRP serum levels in patients with rapid progression of aortic calcification.

Clinical Outcomes of Abdominal Aortic Calcification

Based on data from the coronary circulation it would be expected that abdominal aortic calcification is likely to be associated with cardiovascular events. However, if indeed the coronary calcification score simply reflects atherosclerotic load then there are reasons that the same association may not apply with respect to the abdominal aorta. Firstly, medial calcification is much more common in the abdominal aorta and is not associated with atherosclerosis.[22] Secondly, aortic occlusion is much less common than coronary artery occlusion.[53] Thirdly, AAA is an additional important pathology present within the aorta where calcification may potentially have a protective role with respect to this condition.[75]

Compared to the coronary system, relatively few studies have been carried out to assess abdominal aortic calcification and subsequent outcomes. Seven studies examined the relationship of abdominal aortic calcification to cardiovascular outcomes.[16,29,42,46,52–54] The synthesis of available data was limited due to the variable cardiovascular end-points examined in the studies. We synthesised the data based on cardiovascular events and cardiovascular deaths. Specifically, the cardiovascular events of interest included development of congestive heart failure (CHF), myocardial infarction, stroke or transient ischaemic attacks (TIAs). Cardiovascular mortality was defined as death due to myocardial infarction, stroke or coronary heart disease (CHD). From the seven studies identified, only three presented data in a manner allowing sub-analysis (Table 2).[52–54] In these studies, we differentiated the cardiovascular outcomes based on the severity of abdominal aortic calcification. For example, the study by Walsh *et al.*,[52] high calcification was defined as abdominal aortic calcification (AAC) score >4, while low calcification was AAC scores 0–4.[52] The three studies provided a total of 6862 subjects graded with low or high aortic calcification for whom

Table 2. Abdominal aortic calcification and cardiovascular outcomes

References	Follow-up (years)	Cardiovascular events		Cardiovascular mortality	
		High calcification	Low calcification	High calcification	Low calcification
[52]	22	113/641	51/890		
[53]	22	709/786	335/946	365/786	135/946
[54]	6	133/1718	40/1881		
Total		955/3145 (30%)	426/3717 (11%)	365/786 (46%)	135/946 (14%)

cardiovascular events were recorded.[52–54] All three studies revealed that more severe abdominal aortic calcification was associated with cardiovascular events.[52–54] In the high aortic calcification tertile 30% of patients had a cardiovascular event compared to 11% in the low calcification tertile ($p<0.01$, chi-squared with Yates correction). Data on the association of aortic calcification and cardiovascular deaths was only available from one study which showed a 46% mortality in the high calcification tertile and a 14% mortality in the low calcification tertile (Table 2).

The study by Walsh *et al.*[52] was instrumental in following patients for a period of 22 years. The authors investigated 2467 Framingham Heart Study participants with plain X-ray for an association between congestive heart failure (CHF) and abdominal aortic calcification. In men, the multivariable adjusted risk for CHF was increased for the second (hazard ratio (HR) 1.5; 95% CI 0.9–2.5) and third (HR 2.2; 95% CI 1.3–3.7) tertiles compared to lowest calcification tertile.[52] In women, the second and third tertile in comparison to lowest calcification tertile was HR 1.8 (95% CI 1.1–2.9) and HR 3.2 (95% CI 2.0–5.1), respectively.[52] Wilson *et al.*[53] also investigated the relationship between abdominal aortic calcification and subsequent events over a 20-year period. However, calcification was again only measured by plain X-ray. In this study, events of interest were specified clearly as CHD events (angina pectoris, unstable angina, MI, coronary disease deaths), CVD events (transient ischaemic attacks, stroke death, congestive heart failure) and CVD mortality (death form CHD or cerebrovascular disease)[53]. From multivariate analysis, RR for CHD event for abdominal aortic calcification tertile 3 versus 1 was 1.91 (95% CI 1.48–2.47). The RR for CVD events was 1.70 (95% CI 1.38–2.09), while for CVD mortality RR 2.26 (95% CI 1.66–3.09).[53] Therefore, the presence of abdominal aortic calcification was associated with an increased risk of CHD, CVD and CVD deaths (Fig. 2).[53] Hollander *et al.*[54] investigated the relationship of stroke to abdominal aortic calcification in a very large prospective study of the Rotterdam Study cohort. From Cox regression analysis, the RR for strokes for the highest abdominal aortic calcification tertile was 1.89 (95% CI 1.28–2.80).[54] Although there is strong evidence to support abdominal aortic calcification as a risk factor for adverse cardiovascular outcomes, Niskanen *et al.*[42] failed to show a relationship between aortic calcification and development of myocardial infarction. However, this was a smaller study, with relatively short follow-up in comparison to the other studies.

The larger studies detailed above demonstrate a relationship between aortic calcification and

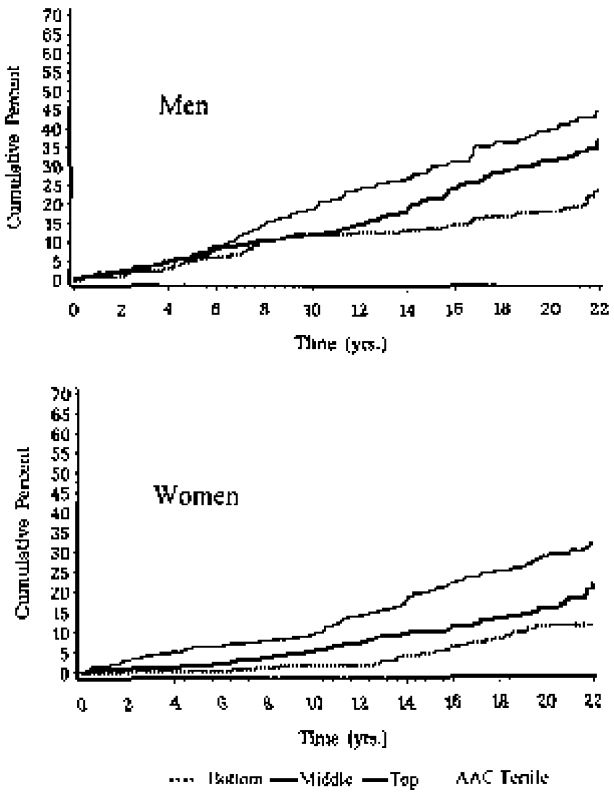

Fig. 2. Age-adjusted incidence of CVD death over a 22-year follow-up period for men and women according to abdominal aortic calcification (AAC) tertile. (Reproduced from Wilson *et al.* with permission).[53]

subsequent cardiovascular events. These likely reflect that the degree of calcification within these arteries is related to the total amount of atherosclerosis present in these patients. Most ischaemic events associated with atherosclerosis appear to result from rupture of the overlying fibrous cap of an atherosclerotic plaque.[76] There is some evidence to support calcification as an atherosclerotic plaque stabilising agent. For example, Hunt *et al.*[77] demonstrated that calcification was present in 48% of stable compared to 34% of unstable atherosclerotic plaques from endarterectomy specimens collected from patients with carotid stenosis.[77] Similarly, aortic arch calcification demonstrated by echocardiogram has been associated with reduced risk of peripheral embolisation.[78] There is similar data from the coronary circulation to show an association between calcification and plaque stability.[5]

Future directions

Aortic calcification while less studied appears to share similar risk factors and clinical significance as coronary aortic calcification. Consequently imaging modalities to quantify aortic calcification as well as serum

markers of vascular calcification may prove to be a useful tool to predict or identify 'at risk' patients. Further studies are required to demonstrate whether vascular calcification is simply a marker of atherosclerotic load or directly influences arterial complications, such as abdominal aortic aneurysm development. However, to facilitate such studies, a simple and widely applicable method to quantify abdominal aortic calcification needs to be developed, which is compatible with the varied imaging modalities used. It is likely that in the future, abdominal aortic calcification may be utilised for effective risk factor modification, by allowing objective assessment of cardiovascular disease progression.

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